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=> d his

     (FILE 'HOME' ENTERED AT 13:32:27 ON 19 NOV 2009)

     FILE 'CAPLUS' ENTERED AT 13:32:37 ON 19 NOV 2009
L1             1 S US 20060189594/PN
                 SELECT RN L1 1-

     FILE 'REGISTRY' ENTERED AT 13:32:57 ON 19 NOV 2009
L2            16 S E1-16
L3             6 S L2 AND 6-6-7/SZ
L4             6 S L3 AND NRS>1
L5             1 S L4 AND C40 H39 N3 O2 S/MF
L6             1 S L4 AND C19 H21 N3 O S/MF
L7             1 S L4 AND C21 H25 N3 O2 S/MF
L8             1 S L4 AND C23 H27 N3 O3 S/MF
L9             1 S L4 AND C28 H31 N3 O2 S/MF
L10            1 S L4 NOT (L5 OR L6 OR L7 OR L8 OR L9)

     FILE 'CAPLUS' ENTERED AT 13:36:00 ON 19 NOV 2009
L11            2 S L5
L12           13 S L6
L13         1410 S L7
L14            3 S L8
L15            3 S L9
L16          302 S L10

     FILE 'REGISTRY' ENTERED AT 13:36:31 ON 19 NOV 2009

     FILE 'CAPLUS' ENTERED AT 13:36:32 ON 19 NOV 2009

     FILE 'REGISTRY' ENTERED AT 13:36:37 ON 19 NOV 2009

     FILE 'CAPLUS' ENTERED AT 13:36:38 ON 19 NOV 2009

     FILE 'REGISTRY' ENTERED AT 13:37:17 ON 19 NOV 2009

     FILE 'CAPLUS' ENTERED AT 13:37:18 ON 19 NOV 2009

     FILE 'REGISTRY' ENTERED AT 13:41:55 ON 19 NOV 2009
L17           10 S L2 NOT L4
L18            2 S L17 AND PYRAN

     FILE 'CAPLUS' ENTERED AT 13:43:14 ON 19 NOV 2009
L19          117 S L18
L20         1613 S L13 OR L16
L21           12 S L12 AND L20
L22           15 S L21 OR L11 OR L14 OR L15

     FILE 'REGISTRY' ENTERED AT 13:46:15 ON 19 NOV 2009
L23       156308 S 6-6-7/SZ
L24      1745443 S 46.383/RID
L25        24901 S L23 AND L24
L26         9254 S L25 AND NRS=3
L27           21 S L26 AND PYRAN
L28            4 S L27 AND C26 H33 N3 O3 S/MF
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     FILE 'CAPLUS' ENTERED AT 13:48:58 ON 19 NOV 2009
L29            2 S L28
L30           16 S L22 OR L29

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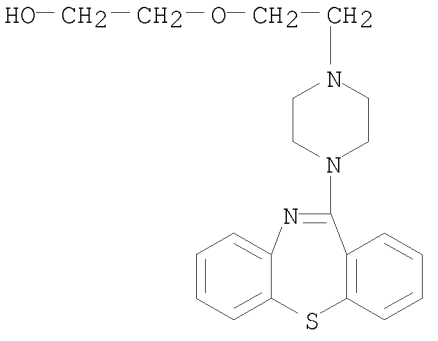
L30 ANSWER 1 OF 16 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2009:756468 CAPLUS
DOCUMENT NUMBER: 151:150475
TITLE: An Improved and Single Pot Process for the Production of Quetiapine Hemifumarate Substantially Free from Potential Impurities
AUTHOR(S): Niphade, Navnath C.; Mali, Anil C.; Pandit, Bhushan S.; Jagtap, Kunal M.; Jadhav, Sanjay A.; Jachak, Madhukar N.; Mathad, Vijayavitthal T.
CORPORATE SOURCE: Department of Process Research and Development, Megafine Pharma (P) Ltd., Nashik, Maharashtra, 422202, India
SOURCE: Organic Process Research & Development (2009), 13(4), 792-797
CODEN: OPRDFK; ISSN: 1083-6160
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB An improved and single pot process for the preparation of Quetiapine hemifumarate, an antipsychotic drug, free from potential impurities was developed, and has overall yield of 80%. The current process suffers from the drawback of potential impurities identified as 11-piperazin-1-yl-dibenzo[b,f][1,4]thiazepine, 2-(4-dibenzo[b,f][1,4]thiazepin-11-ylpiperazin-1-yl)ethanol, dimer, and N-methyl-N-phenyldibenzo[b,f][1,4]thiazapine-11-amine. Elimination of these impurities in the process is achieved by chlorination and in situ condensation of intermediates and stabilizing the pH during workup to obtain a free base, which is further converted to quetiapine hemifumarate salt, free from all these impurities. Different aspects of process development such as scheme selection, optimization of different process parameters, identification, synthesis, origin and control of impurities, and development of an accurate anal. method based on reverse phase HPLC during the development of a scalable process for quetiapine hemifumarate are discussed.
IT 111974-72-2P, Quetiapine Hemifumarate
RL: IMF (Industrial manufacture); PUR (Purification or recovery); PREP (Preparation)
(development and optimization of single pot process for production of Quetiapine hemifumarate and method for impurity removal and HPLC determination)
RN 111974-72-2 CAPLUS
CN Ethanol, 2-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]-, (2E)-2-butenedioate (2:1) (CA INDEX NAME)

CM 1

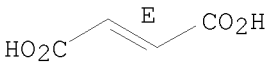
CRN 111974-69-7
CMF C21 H25 N3 O2 S



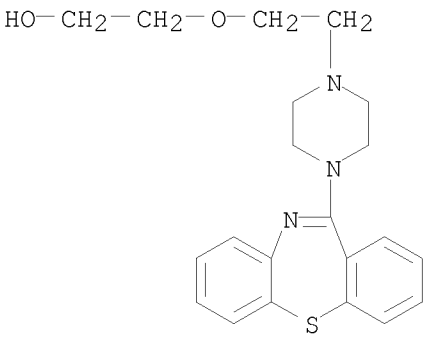
CM 2

CRN 110-17-8
CMF C4 H4 O4

Double bond geometry as shown.

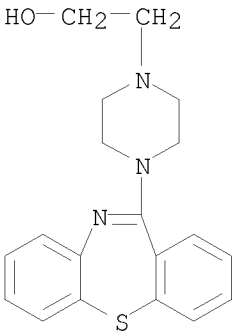


IT 111974-69-7P, Quetiapine
RL: IMF (Industrial manufacture); RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)
(development and optimization of single pot process for production of Quetiapine hemifumarate and method for impurity removal and HPLC determination)
RN 111974-69-7 CAPLUS
CN Ethanol, 2-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]- (CA INDEX NAME)



IT 329216-67-3P, 2-(4-Dibenzo[b,f][1,4]thiazepin-11-ylpiperazin-1-yl)ethanol
RL: ANT (Analyte); REM (Removal or disposal); SPN (Synthetic preparation); ANST (Analytical study); PREP (Preparation); PROC (Process)
(impurity; development and optimization of single pot process for

production of Quetiapine hemifumarate and method for impurity removal and HPLC determination)
RN 329216-67-3 CAPLUS
CN 1-Piperazineethanol, 4-dibenzo[b,f][1,4]thiazepin-11-yl- (CA INDEX NAME)



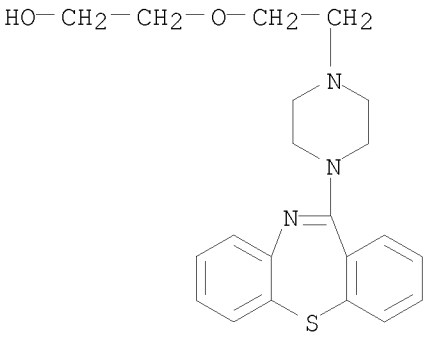
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 2 OF 16 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2009:202755 CAPLUS
DOCUMENT NUMBER: 150:437635
TITLE: In silico methods for predicting metabolism and mass fragmentation applied to quetiapine in liquid chromatography/time-of-flight mass spectrometry urine drug screening
AUTHOR(S): Pelander, Anna; Tyrkko, Elli; Ojanpera, Ilkka
CORPORATE SOURCE: Department of Forensic Medicine, University of Helsinki, FI-00014, Finland
SOURCE: Rapid Communications in Mass Spectrometry (2009), 23(4), 506-514
CODEN: RCMSEF; ISSN: 0951-4198
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

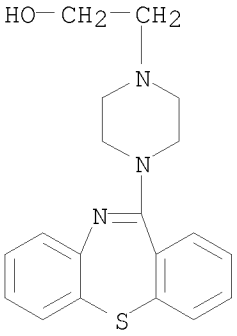
AB Current in silico tools were evaluated for their ability to predict metabolism and mass spectral fragmentation in the context of anal. toxicol. practice. A metabolite prediction program (Lhasa Meteor), a metabolite detection program (Bruker MetaboliteDetect), and a fragmentation prediction program (ACD/MS Fragmenter) were used to assign phase I metabolites of the antipsychotic drug quetiapine in the liquid chromatog./time-of-flight mass spectrometry (LC/TOFMS) accurate mass data from ten autopsy urine samples. In the literature, the main metabolic routes of quetiapine have been reported to be sulfoxidn., oxidation to the corresponding carboxylic acid, N- and O-dealkylation and hydroxylation. Of the 14 metabolites predicted by Meteor, eight were detected by LC/TOFMS in the urine samples with use of MetaboliteDetect software and manual inspection. An addnl. five hydroxy derivs. were detected, but not predicted by Meteor. The fragment structures provided by ACD/MS Fragmenter software confirmed the identification of the metabolites. Mean mass accuracy and isotopic pattern match (SigmaFit) values for the fragments were 2.40 ppm (0.62 mDa) and 0.010, resp. ACD/MS Fragmenter, in particular, allowed metabolites with identical mol. formulas to be differentiated without a need to access the resp. reference stds. or reference spectra. This was well exemplified with the hydroxy/sulfoxy metabolites of quetiapine and their N- and O-dealkylated forms. The procedure resulted in assigning 13 quetiapine metabolites in urine. The present approach is instrumental in developing an extensive database containing exact monoisotopic masses and verified retention times of drugs and their urinary metabolites for LC/TOFMS drug screening.

IT 111974-69-7, Quetiapine
RL: ANT (Analyte); PKT (Pharmacokinetics); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(in silico methods for predicting metabolism and mass fragmentation applied to quetiapine in liquid chromatog./time-of-flight mass spectrometry urine drug screening)

RN 111974-69-7 CAPLUS
CN Ethanol, 2-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]- (CA INDEX NAME)

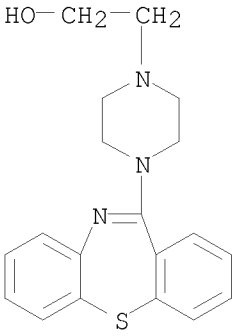


IT 329216-67-3
RL: ANT (Analyte); PRP (Properties); ANST (Analytical study)
(in silico methods for predicting metabolism and mass fragmentation applied to quetiapine in liquid chromatog./time-of-flight mass spectrometry urine drug screening)
RN 329216-67-3 CAPLUS
CN 1-Piperazineethanol, 4-dibenzo[b,f][1,4]thiazepin-11-yl- (CA INDEX NAME)

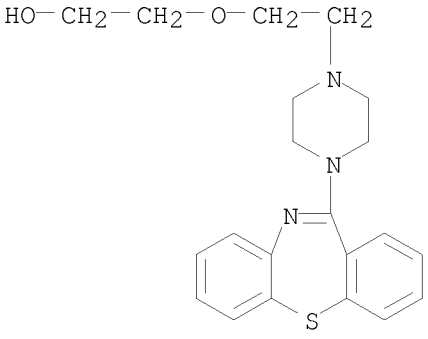


OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 3 OF 16 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2009:94363 CAPLUS
DOCUMENT NUMBER: 150:320645
TITLE: Preliminary evaluation of monolithic column high-performance liquid chromatography with tris(2,2'-bipyridyl)ruthenium(II) chemiluminescence detection for the determination of quetiapine in human body fluids
AUTHOR(S): Bellomarino, Sara A.; Brown, Allyson J.; Conlan, Xavier A.; Barnett, Neil W.
CORPORATE SOURCE: School of Life and Environmental Sciences, Deakin University, Geelong, 3217, Australia
SOURCE: Talanta (2009), 77(5), 1873-1876
CODEN: TLNTA2; ISSN: 0039-9140
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB High-performance liquid chromatog. (HPLC) with tris(2,2'-bipyridyl)ruthenium(II) chemiluminescence detection methodol. is reported for the determination of the atypical antipsychotic drug quetiapine and the observation of its major active and inactive metabolites in human urine and serum. The method uses a monolithic chromatog. column allowing high flow rates of 3 mL min-1 enabling rapid quantification. Flow injection anal. (FIA) with tris(2,2'-bipyridyl)ruthenium(II) chemiluminescence detection and HPLC time of flight mass spectrometry (TOF-MS) were used for the determination of quetiapine in a pharmaceutical preparation to establish its suitability as a calibration standard The limit of detection achieved with FIA was 2 + 10-11 mol L-1 in simple aqueous solution The limits of detection achieved with HPLC were 7 + 10-8 and 2 + 10-10 mol L-1 in urine and serum, resp. The calibration range for FIA was between 5 + 10-9 and 1 + 10-6 mol L-1. The calibration ranges for HPLC were between 1 + 10-7-1 + 10-4 and 1 + 10-8-1 + 10-4 mol L-1 in urine and serum, resp. The quetiapine concns. in patient samples were found to be 3 + 10-6 mol L-1 in urine and 7 + 10-7 mol L-1 in serum. Without the need for preconcn., the HPLC detection limits compared favorably with those in previously published methodologies. The metabolites were identified using HPLC-TOF-MS.
IT 329216-67-3
RL: ANT (Analyte); ANST (Analytical study)
(preliminary evaluation of monolithic column high-performance liquid chromatog. with trisbipyridylruthenium II chemiluminescence detection for determination of quetiapine in human body fluids)
RN 329216-67-3 CAPLUS
CN 1-Piperazineethanol, 4-dibenzo[b,f][1,4]thiazepin-11-yl- (CA INDEX NAME)



IT 111974-69-7, Quetiapine
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(preliminary evaluation of monolithic column high-performance liquid chromatog. with trisbipyridylruthenium II chemiluminescence detection for determination of quetiapine in human body fluids)
RN 111974-69-7 CAPLUS
CN Ethanol, 2-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]- (CA INDEX NAME)



REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

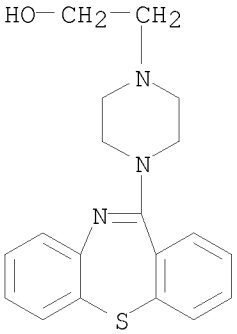
L30 ANSWER 4 OF 16 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2008:1233138 CAPLUS
DOCUMENT NUMBER: 151:101139
TITLE: Purification of HEEP
AUTHOR(S): Anon.
CORPORATE SOURCE: USA
SOURCE: IP.com Journal (2008), 8(8A), 15 (No. IPCOM000173019D), 24 Jul 2008
CODEN: IJPOBX; ISSN: 1533-0001
PUBLISHER: IP.com, Inc.
DOCUMENT TYPE: Journal; Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
IP 173019D		20080724	IP 2008-173019D	20080724

PRIORITY APPLN. INFO.: IP 2008-173019D 20080724
OTHER SOURCE(S): CASREACT 151:101139

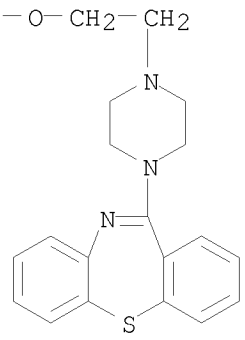
AB A method for the purification of the title compound [i.e., HEEP, 2-[2-(1-piperazinyl)ethoxy]ethanol] involves the application of high-vacuum fractional distillation A reaction of this purified reactant with 11-chlorodibenzo[b,f][1,4]thiazepine gave 2-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]ethanol (2E)-2-butenedioate (2:1) (i.e., quetiapine fumarate).

IT 329216-67-3P, 4-(Dibenzo[b,f][1,4]thiazepin-11-yl)-1-piperazineethanol
RL: BYP (Byproduct); PUR (Purification or recovery); PREP (Preparation)
(preparation of [[(dibenzo[b,f][1,4]thiazepinyl)piperazinyl]ethoxy]ethanol fumarate)
RN 329216-67-3 CAPLUS
CN 1-Piperazineethanol, 4-dibenzo[b,f][1,4]thiazepin-11-yl- (CA INDEX NAME)



IT 111974-69-7P, 2-[2-(4-Dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]ethanol
RL: PUR (Purification or recovery); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of [[(dibenzo[b,f][1,4]thiazepinyl)piperazinyl]ethoxy]ethanol fumarate by reaction of (chloro)dibenzo[b,f][1,4]thiazepine with [(piperazinyl)ethoxy]ethanol)
RN 111974-69-7 CAPLUS

CN Ethanol, 2-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]- (CA INDEX NAME)



IT 111974-72-2P, Quetiapine fumarate
RL: PUR (Purification or recovery); SPN (Synthetic preparation); PREP (Preparation)
(preparation of [[(dibenzo[b,f][1,4]thiazepinyl)piperazinyl]ethoxy]ethanol fumarate by reaction of (chloro)dibenzo[b,f][1,4]thiazepine with [(piperazinyl)ethoxy]ethanol)

RN 111974-72-2 CAPLUS

CN Ethanol, 2-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]-, (2E)-2-butenedioate (2:1) (CA INDEX NAME)

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CRN 111974-69-7
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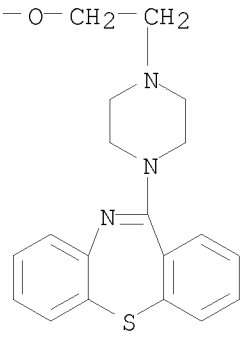
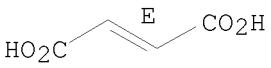


CM 2

CRN 110-17-8
CMF C4 H4 O4

Double bond geometry as shown.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CO2H

L30 ANSWER 5 OF 16 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2008:674294 CAPLUS
DOCUMENT NUMBER: 149:32336
TITLE: Preparation of dibenzothiazepine derivatives as antagonists of multiple neurotransmitter receptors
INVENTOR(S): Tung, Roger; Harbeson, Scott
PATENT ASSIGNEE(S): Concert Pharmaceuticals Inc., USA
SOURCE: PCT Int. Appl., 35pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2008066620	A2	20080605	WO 2007-US22338	20071019
WO 2008066620	A3	20081113		

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RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA

PRIORITY APPLN. INFO.: US 2006-853209P P 20061020
OTHER SOURCE(S): MARPAT 149:32336
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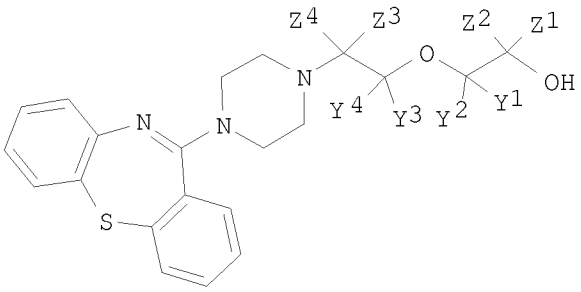

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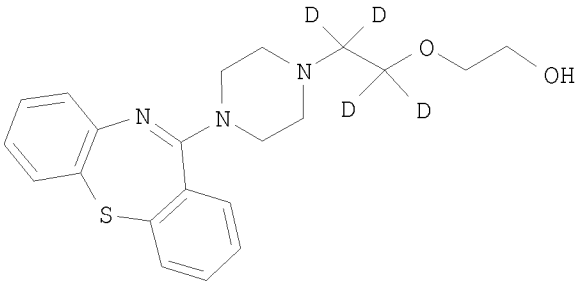


II

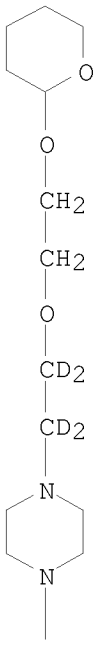
AB This title compds. with general formula I [wherein Z1-Z4 = independently hydrogen or deuterium; Y1-Y4 = independently hydrogen, deuterium, or fluorine; and at least one of Z1-Z4 is deuterium] or pharmaceutically acceptable acid addition salts, solvates, hydrates, or polymorphs thereof were prepared as antagonists of multiple neurotransmitter receptors in brain, for the treatment of diseases and conditions beneficially from the inhibition of serotonergic 5HT1A and 5HT2 receptors, dopaminergic D1 and D2 receptors, histaminergic H1 receptors, or adrenergic α1 and α2 receptors. For example, compound II was prepared in a multi-step synthesis. I can be used for the treatment of a patient suffering from or susceptible to a disease of condition selected from schizophrenia, schizo-affective disorders, mania (manic disorder), bipolar I disorder, bipolar II disorder, depression associated with bipolar disorders, etc.

IT 1031703-39-5P 1031703-40-8P 1031703-41-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of dibenzothiazepine derivs. as antagonists of multiple neurotransmitter receptors)

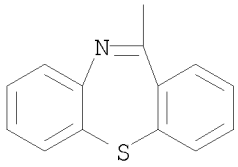
RN 1031703-39-5 CAPLUS

CN Dibenzo[b,f][1,4]thiazepine, 11-[4-[2-[2-[(tetrahydro-2H-pyran-2-yl)oxy]ethoxy]ethyl-1,1,2,2-d4]-1-piperazinyl]- (CA INDEX NAME)

PAGE 1-A

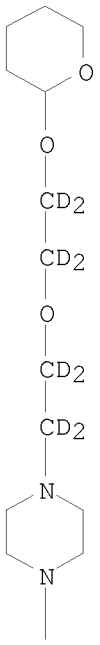


PAGE 2-A



RN 1031703-40-8 CAPLUS
CN Dibenzo[b,f][1,4]thiazepine, 11-[4-[2-[2-[(tetrahydro-2H-pyran-2-yl)oxy]ethoxy-1,1,2,2-d4]ethyl-1,1,2,2-d4]-1-piperazinyl]- (CA INDEX NAME)

PAGE 1-A



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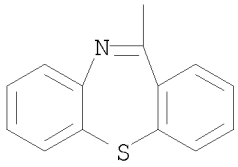
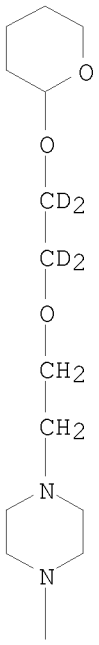
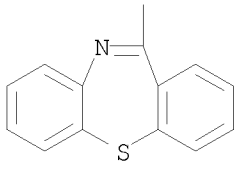


RN 1031703-41-9 CAPLUS
CN Dibenzo[b,f][1,4]thiazepine, 11-[4-[2-[2-[(tetrahydro-2H-pyran-2-yl)oxy]ethoxy-1,1,2,2-d4]ethyl]-1-piperazinyl]- (CA INDEX NAME)

PAGE 1-A



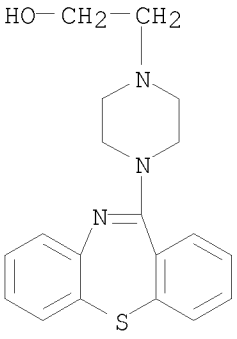
PAGE 2-A



L30 ANSWER 6 OF 16 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2008:79719 CAPLUS
DOCUMENT NUMBER: 148:363066
TITLE: Identification, isolation, synthesis and characterization of impurities of quetiapine fumarate
AUTHOR(S): Bharathi, Ch.; Prabahar, K. J.; Prasad, Ch. S.; Srinivasa Rao, M.; Trinadhachary, G. N.; Handa, V. K.; Dandala, Ramesh; Naidu, A.
CORPORATE SOURCE: Research Centre, Aurobindo Pharma Ltd., Hyderabad, 500072, India
SOURCE: Pharmazie (2008), 63(1), 14-19
CODEN: PHARAT; ISSN: 0031-7144
PUBLISHER: Govi-Verlag Pharmazeutischer Verlag GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 148:363066
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

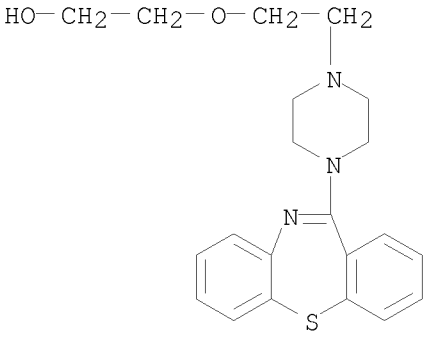
AB In the process for the preparation of quetiapine fumarate (1), six unknown impurities (I-VI) and one known impurity (intermediate) were identified ranging from 0.05-0.15% by reverse-phase HPLC. These impurities were isolated from crude samples using reverse-phase preparative HPLC and characterized based on the spectral data. The known impurity was an intermediate, 11-piperazinyldibenzo[b,f][1,4]thiazepine(piperazinylthiazepine). The structures were established unambiguously by independent synthesis and coinjection in HPLC to confirm the retention times. To the best of authors' knowledge, these impurities have not been reported before. Structural elucidation of all impurities by spectral data (1H NMR, 13C NMR, MS and IR), synthesis and formation of these impurities are discussed in detail.
IT 329216-67-3P
RL: OCU (Occurrence, unclassified); SPN (Synthetic preparation); OCCU (Occurrence); PREP (Preparation)
(identification, isolation, synthesis and characterization of impurities of quetiapine fumarate)
RN 329216-67-3 CAPLUS
CN 1-Piperazineethanol, 4-dibenzo[b,f][1,4]thiazepin-11-yl- (CA INDEX NAME)



IT 111974-72-2, Quetiapine fumarate
RL: RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(identification, isolation, synthesis and characterization of impurities of quetiapine fumarate)
RN 111974-72-2 CAPLUS
CN Ethanol, 2-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]-, (2E)-2-butenedioate (2:1) (CA INDEX NAME)

CM 1

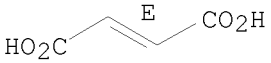
CRN 111974-69-7
CMF C21 H25 N3 O2 S



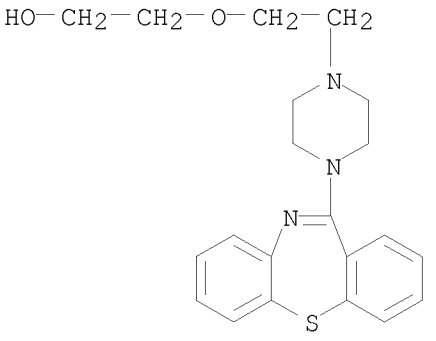
CM 2

CRN 110-17-8
CMF C4 H4 O4

Double bond geometry as shown.



IT 111974-69-7P
RL: RGT (Reagent); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(identification, isolation, synthesis and characterization of impurities of quetiapine fumarate)
RN 111974-69-7 CAPLUS
CN Ethanol, 2-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]- (CA INDEX NAME)



OS.CITING REF COUNT:	2	THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT:	6	THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 7 OF 16 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2007:249111 CAPLUS
DOCUMENT NUMBER: 147:541911
TITLE: Process for the preparation of quetiapine, a dopamine antagonist
INVENTOR(S): Deshpande, Pandurang Balwant
PATENT ASSIGNEE(S): Orichid Chemicals & Pharmaceuticals Ltd., India
SOURCE: Indian Pat. Appl., 26pp.
CODEN: INXXBQ
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

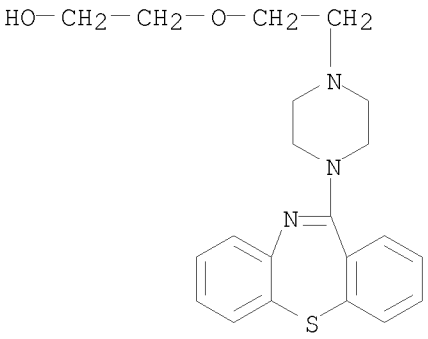
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
IN 2003CH00804	A	20051118	IN 2003-CH804	20031006
PRIORITY APPLN. INFO.:			IN 2003-CH804	20031006

OTHER SOURCE(S): CASREACT 147:541911; MARPAT 147:541911
GI

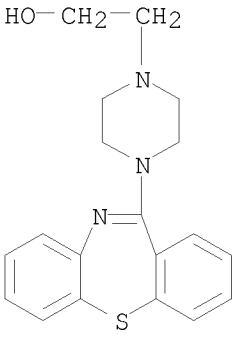
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention relates to a process for the preparation of biol. active thiazepine derivative I [R1 = (CH2)2O(CH2)2OH, (CH2)2OH, (CH2)2Cl]. The present invention more particularly relates to an improved process for the preparation of quetiapine [I; R1 = (CH2)2O(CH2)2OH], a dopamine antagonist. Thus, reaction of 2-fluoronitrobenzene with thiosalicylic acid followed by converting the resulting 2-(2-nitrophenylthio)benzoic acid into acid chloride, reacting the acid chloride with 1-[2-(2-hydroxyethoxy)ethyl]piperazine, reduction of II, and cyclization of III afforded quetiapine [I; R1 = (CH2)2O(CH2)2OH].

IT 111974-69-7P 329216-67-3P
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(process for the preparation of quetiapine, a dopamine antagonist)
RN 111974-69-7 CAPLUS
CN Ethanol, 2-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]- (CA INDEX NAME)



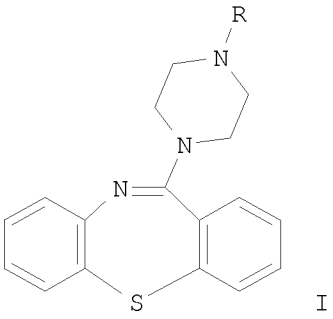
RN 329216-67-3 CAPLUS
CN 1-Piperazineethanol, 4-dibenzo[b,f][1,4]thiazepin-11-yl- (CA INDEX NAME)



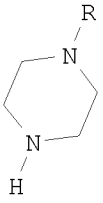
L30 ANSWER 8 OF 16 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2006:1114869 CAPLUS
DOCUMENT NUMBER: 145:397560
TITLE: Condensation process for the preparation of 11-[4-(substituted)-1-piperazinyl]dibenzo[b,f]-1,4-thiazepines from piperazines and 10H-dibenzo[b,f][1,4]thiazepin-11-one in the presence of titanium tetraalkoxides
INVENTOR(S): Comelv, Alexander Chris; Verdaguer Espaulella, Francesc Xavier; Rafecas, Jane Llorenc; Domingo Coto, Antonio
PATENT ASSIGNEE(S): Union Quimico-Farmaceutica S.A., Spain
SOURCE: Span., 16pp.
CODEN: SPXXAD
DOCUMENT TYPE: Patent
LANGUAGE: Spanish
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
ES 2234447	A1	20050616	ES 2005-513	20050307
ES 2234447	B1	20060301		
WO 2006094549	A1	20060914	WO 2005-EP14055	20051221
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
EP 1856073	A1	20071121	EP 2005-850361	20051221
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, YU				
US 20080171869	A1	20080717	US 2007-817884	20070906
NO 2007005071	A	20071128	NO 2007-5071	20071008

PRIORITY APPLN. INFO.: ES 2005-513 A 20050307
WO 2005-EP14055 W 20051221
OTHER SOURCE(S): CASREACT 145:397560; MARPAT 145:397560
GI



I



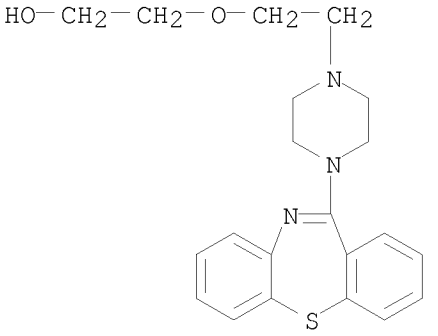
II

AB 11-[4-(Substituted)-1-piperazinyl]dibenzo[b,f][1,4]thiazepines [I; R = (CH2)2OH, (CH2)2O(CH2)2OH; e.g., quetiapine] are prepared by the condensation of piperazines [II; e.g., 1-(2-hydroxyethoxy)ethyl)piperazine] with 10H-dibenzo[b,f]-1,4-thiazepin-11-one in the presence of titanium tetraalkoxides Ti(OR1)4 [R1 = (un)branched C1-8 alkyl; e.g., titanium tetraisopropoxide] which may optionally be salified with acids.

IT 111974-69-7P, Quetiapine
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(condensation process for the preparation of 11-(4-substituted-1-piperazinyl)dibenzo[b,f]-1,4-thiazepines from piperazines and 10H-dibenzo[b,f][1,4]thiazepin-11-one in the presence of titanium tetraalkoxides)

RN 111974-69-7 CAPLUS

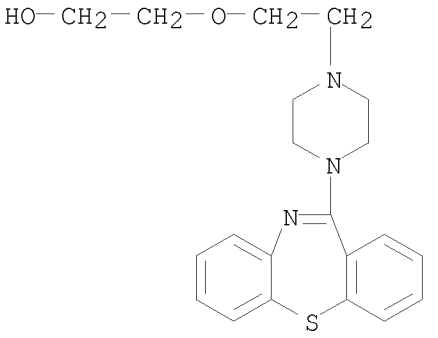
CN Ethanol, 2-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]- (CA INDEX NAME)



IT 111974-72-2P, Quetiapine hemifumarate 329216-67-3P
RL: SPN (Synthetic preparation); PREP (Preparation)
(condensation process for the preparation of 11-(4-substituted-1-piperazinyl)dibenzo[b,f]-1,4-thiazepines from piperazines and 10H-dibenzo[b,f][1,4]thiazepin-11-one in the presence of titanium tetraalkoxides)
RN 111974-72-2 CAPLUS
CN Ethanol, 2-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]-, (2E)-2-butenedioate (2:1) (CA INDEX NAME)

CM 1

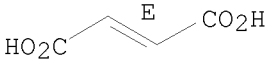
CRN 111974-69-7
CMF C21 H25 N3 O2 S



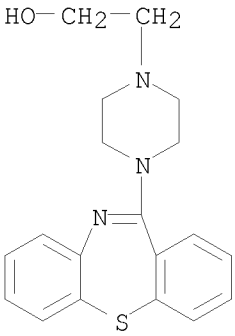
CM 2

CRN 110-17-8
CMF C4 H4 O4

Double bond geometry as shown.



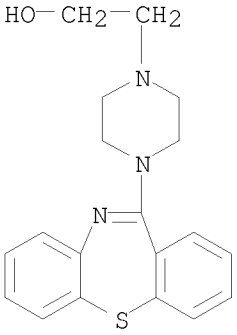
RN 329216-67-3 CAPLUS
CN 1-Piperazineethanol, 4-dibenzo[b,f][1,4]thiazepin-11-yl- (CA INDEX NAME)



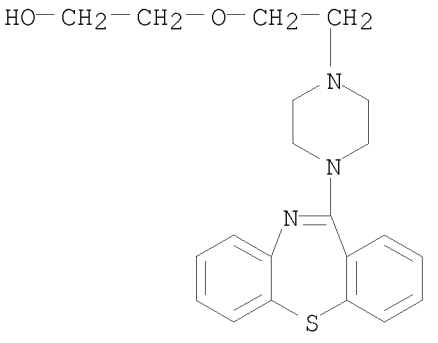
L30 ANSWER 9 OF 16 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2006:684487 CAPLUS
DOCUMENT NUMBER: 145:327595
TITLE: In vitro studies on quetiapine metabolism using the substrate depletion approach with focus on drug-drug interactions
AUTHOR(S): Hasselstroem, Joergen; Linnet, Kristian
CORPORATE SOURCE: Centre for Basic Psychiatric Research, Aarhus University Hospital, Den.
SOURCE: Drug Metabolism and Drug Interactions (2006), Volume Date 2005, 21(3-4), 187-211
CODEN: DMDIEQ; ISSN: 0792-5077
PUBLISHER: Freund Publishing House Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The metabolism of the atypical antipsychotic quetiapine was investigated by in vitro methods. Pharmacokinetic parameters were determined in human liver microsomes and recombinant cytochrome P 450 measuring substrate depletion and product formation. The cytochrome P 450 isoenzymes CYP3A4 and CYP2D6 displayed activity towards quetiapine. The isoenzyme CYP2D6 played a minor role in the metabolism of quetiapine as CYP3A4 contributed 89% to the overall metabolism A Km value of 18 μM was determined by substrate depletion, suggesting linear kinetics under therapeutic conditions. Drugs known to inhibit CYP3A4, such as ketoconazole and nefazodone, displayed almost complete inhibition at low concns., whereas inhibitors of CYP2D6 do not seem to have a clin. relevant effect.

IT 329216-67-3
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(in vitro studies on quetiapine metabolism using the substrate depletion approach with focus on drug-drug interactions)
RN 329216-67-3 CAPLUS
CN 1-Piperazineethanol, 4-dibenzo[b,f][1,4]thiazepin-11-yl- (CA INDEX NAME)



IT 111974-69-7, Quetiapine
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); BIOL (Biological study)
(in vitro studies on quetiapine metabolism using the substrate depletion approach with focus on drug-drug interactions)
RN 111974-69-7 CAPLUS
CN Ethanol, 2-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]- (CA INDEX NAME)

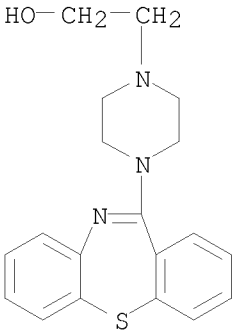


REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

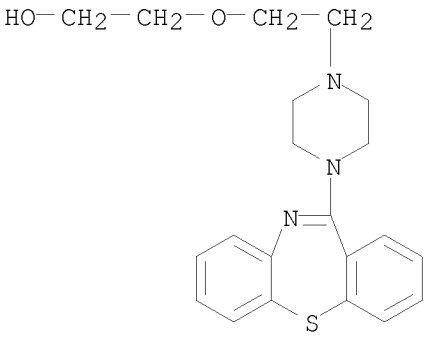
L30 ANSWER 10 OF 16 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2006:238901 CAPLUS
DOCUMENT NUMBER: 144:292785
TITLE: Process for preparation of 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]dibenzo[b,f][1,4]thiazepine (Quetiapine) from 2-amino-2'-carboxydiphenyl sulfide and 1-hydroxyethoxyethylpiperazine.
INVENTOR(S): Pathak, Shailendra; Sharma, Jitendra; Kaushik, Geetesh; Thaper, Rajesh Kumar; Dubey, Sushil Kumar
PATENT ASSIGNEE(S): Jubilant Organosys Limited, India
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006027789	A1	20060316	WO 2004-IN281	20040908
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
IN 2006DN04348	A	20070713	IN 2006-DN4348	20060727
PRIORITY APPLN. INFO.:			WO 2004-IN281 W	20040908

OTHER SOURCE(S): CASREACT 144:292785
AB A process for preparation of Quetiapine comprises reaction of 2-amino-2'-carboxydiphenyl sulfide with a phosphorus halide or oxyhalide to give an iminohalide which is treated with 1-hydroxyethoxyethylpiperazine.
IT 329216-67-3P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of Quetiapine from aminocarboxydiphenyl sulfide and 1-hydroxyethoxyethylpiperazine)
RN 329216-67-3 CAPLUS
CN 1-Piperazineethanol, 4-dibenzo[b,f][1,4]thiazepin-11-yl- (CA INDEX NAME)



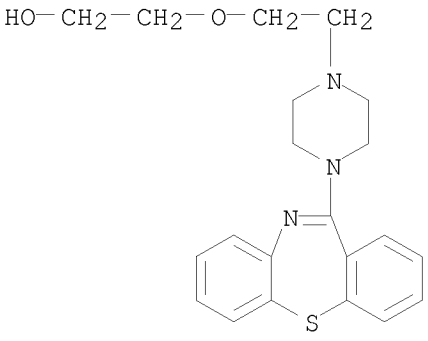
IT 111974-69-7P, Quetiapine 111974-72-2P, Quetiapine hemifumarate
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of Quetiapine from aminocarboxydiphenyl sulfide and 1-hydroxyethoxyethylpiperazine)
RN 111974-69-7 CAPLUS
CN Ethanol, 2-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]- (CA INDEX NAME)



RN 111974-72-2 CAPLUS
CN Ethanol, 2-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]-, (2E)-2-butenedioate (2:1) (CA INDEX NAME)

CM 1

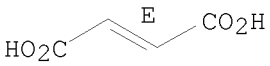
CRN 111974-69-7
CMF C21 H25 N3 O2 S



CM 2

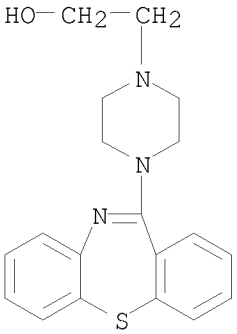
CRN 110-17-8
CMF C4 H4 O4

Double bond geometry as shown.

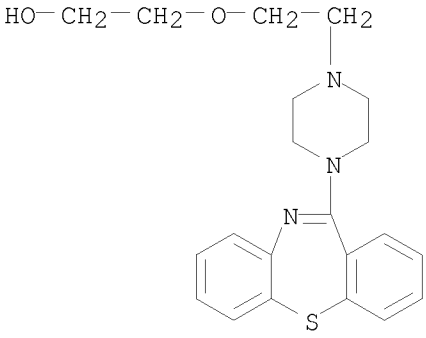


OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 11 OF 16 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2006:72863 CAPLUS
DOCUMENT NUMBER: 145:55319
TITLE: Effects of cytochrome P450 3A modulators ketoconazole and carbamazepine on quetiapine pharmacokinetics
AUTHOR(S): Grimm, Scott W.; Richtand, Neil M.; Winter, Helen R.; Stams, Karen R.; Reele, Stots B.
CORPORATE SOURCE: AstraZeneca Pharmaceuticals LP, Wilmington, DE, USA
SOURCE: British Journal of Clinical Pharmacology (2006), 61(1), 58-69
CODEN: BCPHBM; ISSN: 0306-5251
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Aims To explore the potential for drug interactions on quetiapine pharmacokinetics using in vitro and in vivo assessments. Methods The CYP enzymes responsible for quetiapine metabolite formation were assessed using recombinant expressed CYPs and CYP-selective inhibitors. P-glycoprotein (Pgp) transport was tested in MDCK cells expressing the human MDR1 gene. The effects of CYP3A4 inhibition were evaluated clin. in 12 healthy volunteers that received 25 mg quetiapine before and after 4 days of treatment with ketoconazole 200 mg daily. To assess CYP3A4 induction in vivo, 18 patients with psychiatric disorders were titrated to steady-state quetiapine levels (300 mg twice daily), then titrated to 600 mg daily carbamazepine for 2 wk. Results CYP3A4 was found to be responsible for formation of quetiapine sulfoxide and N- and O-desalkylquetiapine and not a Pgp substrate. In the clin. studies, ketoconazole increased mean quetiapine plasma Cmax by 3.35-fold, from 45 to 150 ng ml-1 (mean Cmax ratio 90% CI 2.51, 4.47) and decreased its clearance (Cl/F) by 84%, from 138 to 22 l h-1 (mean ratio 90% CI 0.13, 0.20). Carbamazepine decreased quetiapine plasma Cmax by 80%, from 1042 to 205 ng ml-1 (mean Cmax ratio 90% CI 0.14, 0.28) and increased its clearance 7.5-fold, from 65 to 483 l h-1 (mean ratio 90% CI 6.04, 9.28). Conclusions Cytochrome P 450 3A4 is a primary enzyme responsible for the metabolic clearance of quetiapine. Quetiapine pharmacokinetics were affected by concomitant administration of ketoconazole and carbamazepine, and therefore other drugs and ingested natural products that strongly modulate the activity or expression of CYP3A4 would be predicted to change exposure to quetiapine.
IT 329216-67-3
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ketoconazole decreased formation of quetiapine metabolite O-desalkylquetiapine in healthy human)
RN 329216-67-3 CAPLUS
CN 1-Piperazineethanol, 4-dibenzo[b,f][1,4]thiazepin-11-yl- (CA INDEX NAME)



IT 111974-69-7, Quetiapine
RL: PKT (Pharmacokinetics); BIOL (Biological study)
(ketoconazole increased Cmax, AUC, t1/2, decreased CL/F of quetiapine in healthy human, carbamazepine decreased Cmax, AUC, tmax, increased CL/F of quetiapine in patient with psychiatric disorder)
RN 111974-69-7 CAPLUS
CN Ethanol, 2-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]-
(CA INDEX NAME)

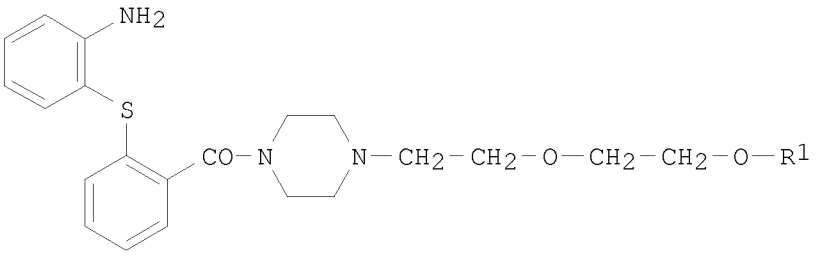


OS.CITING REF COUNT: 18 THERE ARE 18 CAPLUS RECORDS THAT CITE THIS RECORD (18 CITINGS)
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

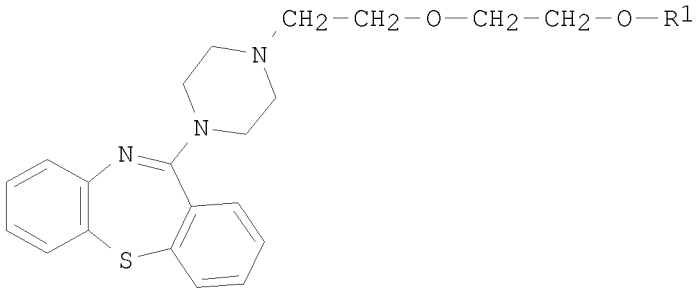
L30 ANSWER 12 OF 16 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:325696 CAPLUS
DOCUMENT NUMBER: 142:392444
TITLE: Preparation of quetiapine
INVENTOR(S): Deshpande, Pandurang Balwant; Holkar, Anil Ganpat; Gudaparthi, Omprakash; Kumar, Jothi Dinesh
PATENT ASSIGNEE(S): Orchid Chemicals & Pharmaceuticals Ltd., India
SOURCE: U.S. Pat. Appl. Publ., 9 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 20050080072	A1	20050414	US 2004-925941		20040826
IN 2003CH00695	A	20051118	IN 2003-CH695		20030901
PRIORITY APPLN. INFO.:			IN 2003-CH695	A	20030901
			US 2004-534100P	P	20040105

OTHER SOURCE(S): CASREACT 142:392444
GI



I



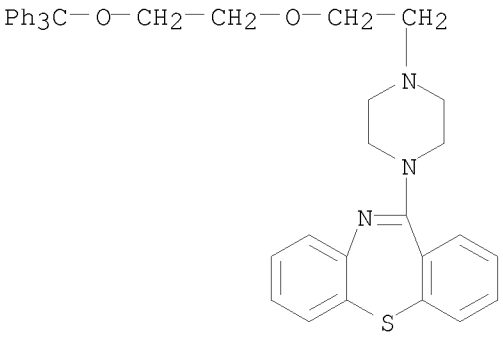
II

AB Preparation of quetiapine via the Lewis acid catalyzed cyclization of aminophenyl I [R1 = alc. protecting group] was disclosed. For example, phosphorus oxychloride (25 mL) was added slowly to a solution of aminophenyl I [25 g; R1 = COMe] in toluene (25 mL). The reaction was heated at reflux for 5-6 h, to afford after work-up, the acetate ester of quetiapine II [R1 =COMe]. Of note, the invention relates to an improved process for the

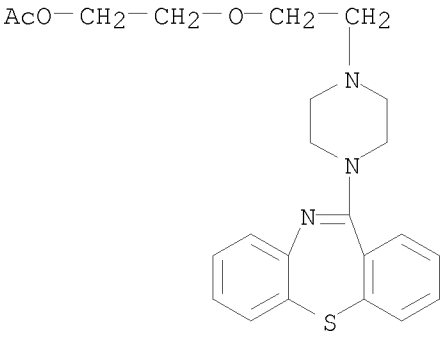
preparation of the dibenzo[b,f][1,4]thiazepine ring of quetiapine.

IT 844639-06-1P 844639-07-2P 844639-08-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of quetiapine)

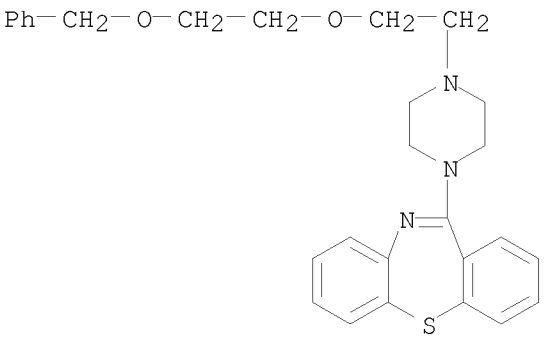
RN 844639-06-1 CAPLUS
CN Dibenzo[b,f][1,4]thiazepine, 11-[4-[2-[2-(triphenylmethoxy)ethoxy]ethyl]-1-piperazinyl]- (CA INDEX NAME)



RN 844639-07-2 CAPLUS
CN Ethanol, 2-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]-, 1-acetate (CA INDEX NAME)



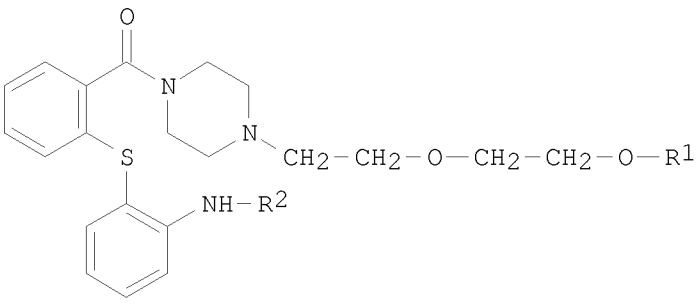
RN 844639-08-3 CAPLUS
CN Dibenzo[b,f][1,4]thiazepine, 11-[4-[2-[2-(phenylmethoxy)ethoxy]ethyl]-1-piperazinyl]- (CA INDEX NAME)



L30 ANSWER 13 OF 16 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:283479 CAPLUS
DOCUMENT NUMBER: 142:355289
TITLE: Preparation of quetiapine via the cyclization of 2-(2-aminophenylthio)benzamides
INVENTOR(S): Rummakko, Petteri; Huhta, Soini; Grumann, Arne
PATENT ASSIGNEE(S): Fermion Oy, Finland
SOURCE: PCT Int. Appl., 18 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005028458	A1	20050331	WO 2004-FI560	20040923
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2538745	A1	20050331	CA 2004-2538745	20040923
EP 1664007	A1	20060607	EP 2004-767074	20040923
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, HR				
JP 2007505864	T	20070315	JP 2006-526653	20040923
US 20070111987	A1	20070517	US 2007-572409	20070116
PRIORITY APPLN. INFO.:			US 2003-504981P	P 20030923
			WO 2004-FI560	W 20040923

OTHER SOURCE(S): CASREACT 142:355289
GI



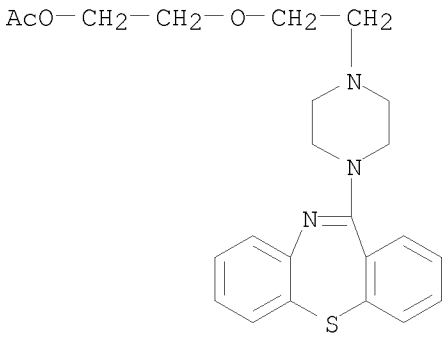
I

AB Preparation of quetiapine via the cyclization of title compds. I [R1 = hydroxyl protecting group, e.g., acetyl, benzoyl, pivaloyl, etc.; R2 = H, amino protecting group, e.g., acetyl, pivaloyl, benzyl] was disclosed. For example, phosphoric trichloride mediated cyclization of acetate I (R1 = COMe; R2 = COMe), afforded the acetate of quetiapine. Of note, phosphorus oxychloride is claimed to be an effective regent for the cyclization of title compds. I.

IT 844639-07-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of quetiapine via the cyclization of aminophenylthiobenzamides)

RN 844639-07-2 CAPLUS

CN Ethanol, 2-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]-, 1-acetate (CA INDEX NAME)



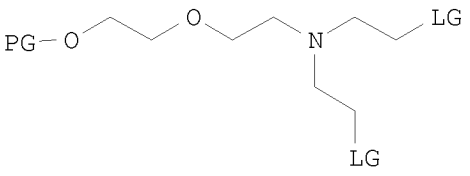
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 14 OF 16 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:283478 CAPLUS
DOCUMENT NUMBER: 142:355288
TITLE: Preparation of quetiapine via the cyclization of N,N-bis(2-haloethyl)ethanamines and dibenzo(b,f)[1,4]thiazepin-1-ylamine
INVENTOR(S): Grumann, Arne; Huhta, Soini; Rummakko, Petteri
PATENT ASSIGNEE(S): Fermion Oy, Finland
SOURCE: PCT Int. Appl., 14 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005028457	A1	20050331	WO 2004-FI559	20040923

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2003-504983P P 20030923
OTHER SOURCE(S): CASREACT 142:355288; MARPAT 142:355288
GI



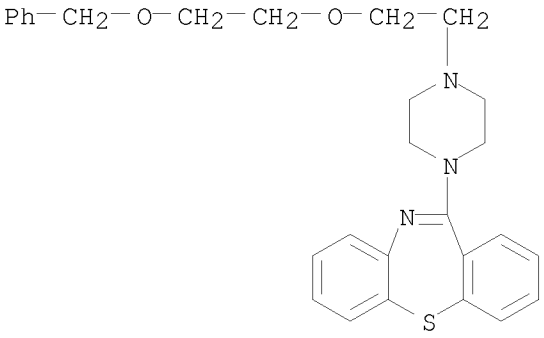
I

AB Preparation of quetiapine via the N-alkylation of dibenzo(b,f)[1,4]thiazepin-1-ylamine with title compds. I [PG = protecting group; LG = leaving group, e.g, halo, CF3, p-toluenesulfonyl, etc.] was disclosed. For example, NaOH mediated N-alkylation of dibenzo(b,f)[1,4]thiazepin-1-ylamine with ethanamine I [PG = CH2Ph; LG = Cl] afforded the benzyl ester of quetiapine in 91% yield.
IT 844639-08-3P 848888-35-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of quetiapine via the cyclization of N,N-bis(2-haloethyl)ethanamines and

dibenzo(b,f)[1,4]thiazepin-1-ylamine)

RN 844639-08-3 CAPLUS

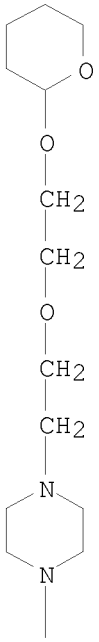
CN Dibenzo[b,f][1,4]thiazepine, 11-[4-[2-[2-(phenylmethoxy)ethoxy]ethyl]-1-piperazinyl]- (CA INDEX NAME)



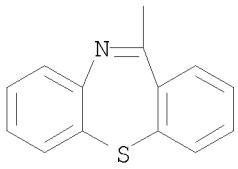
RN 848888-35-7 CAPLUS

CN Dibenzo[b,f][1,4]thiazepine, 11-[4-[2-[2-[(tetrahydro-2H-pyran-2-yl)oxy]ethoxy]ethyl]-1-piperazinyl]- (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



OS.CITING REF COUNT:	2	THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT:	7	THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 15 OF 16 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:141066 CAPLUS
DOCUMENT NUMBER: 142:240472
TITLE: Procedure for preparing a pharmaceutically active compound
INVENTOR(S): Puig Torres, Salvador; Herbera Espinal, Reyes; Dalmases Barjoan, Pere
PATENT ASSIGNEE(S): Laboratorios Vita, S. A., Spain
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005014590	A2	20050217	WO 2004-IB2527	20040727
WO 2005014590	A3	20050506		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
ES 2223294	A1	20050216	ES 2003-1922	20030808
ES 2223294	B2	20051001		
EP 1660468	A2	20060531	EP 2004-744176	20040727
EP 1660468	B1	20070718		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				
JP 2007501837	T	20070201	JP 2006-523068	20040727
AT 367383	T	20070815	AT 2004-744176	20040727
ES 2290734	T3	20080216	ES 2004-744176	20040727
US 20060189594	A1	20060824	US 2006-566413	20060130
KR 2006087506	A	20060802	KR 2006-702638	20060207
KR 864799	B1	20081023		

PRIORITY APPLN. INFO.: ES 2003-1922 A 20030808
WO 2004-IB2527 W 20040727
OTHER SOURCE(S): CASREACT 142:240472; MARPAT 142:240472
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

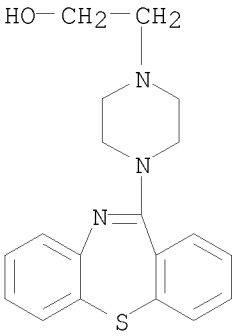
AB The invention relates to a procedure for preparing quetiapine (I) by reaction between dibenzothiazepine II and a compound P-OCH2CH2X [P = alc. protective group resistant to alkaline conditions; especially ethers, e.g., tetrahydropyranyl, CH2Ph, trityl; X = leaving group, e.g., halogen, mesylate, triflate,

nonaflate, tresylate, tosylate, brosylate, nosylate], in the presence of a base, followed by a step of deprotection of ether III and, optionally, obtaining a pharmaceutically acceptable salt thereof. Said procedure permits the obtaining of quetiapine with a high degree of purity under soft temperature conditions, with short reaction times and avoiding the use of toxic solvents.

IT 329216-67-3, 2-[4-(Dibenzo[b,f][1,4]thiazepin-11-yl)piperazin-1-yl]ethanol
RL: RCT (Reactant); RACT (Reactant or reagent)
(etherification of, with (chloroethoxy)tetrahydropyran and analogs; procedure for preparing quetiapine from a dibenzothiazepine piperazinoethanol derivative)

RN 329216-67-3 CAPLUS

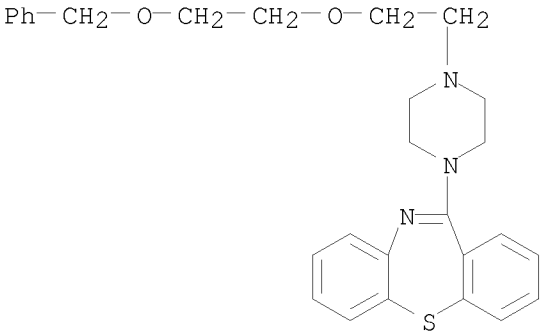
CN 1-Piperazineethanol, 4-dibenzo[b,f][1,4]thiazepin-11-yl- (CA INDEX NAME)



IT 844639-08-3P, 11-[4-[2-(2-Benzyloxyethoxy)ethyl]piperazin-1-yl]dibenzo[b,f][a,4]thiazepine
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and acetolysis of; procedure for preparing quetiapine from a dibenzothiazepine piperazinoethanol derivative)

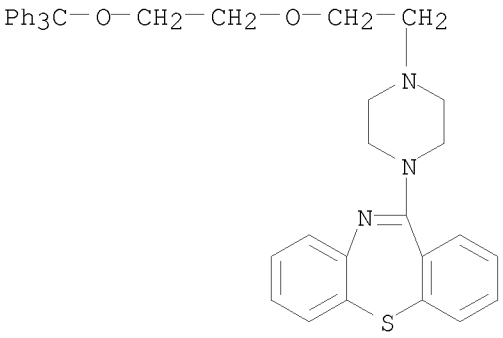
RN 844639-08-3 CAPLUS

CN Dibenzo[b,f][1,4]thiazepine, 11-[4-[2-[2-(phenylmethoxy)ethoxy]ethyl]-1-piperazinyl]- (CA INDEX NAME)

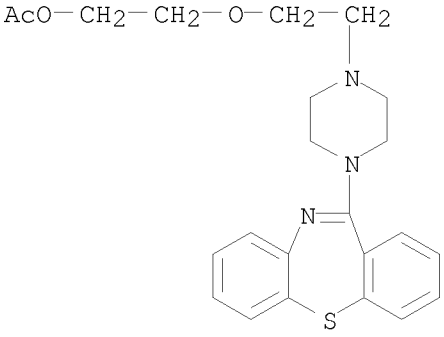


IT 844639-06-1P, 11-[4-[2-(2-Trityloxyethoxy)ethyl]piperazin-1-yl]dibenzo[b,f][a,4]thiazepine

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and acid hydrolysis of; procedure for preparing quetiapine from a
dibenzothiazepine piperazinoethanol derivative)
RN 844639-06-1 CAPLUS
CN Dibenzo[b,f][1,4]thiazepine, 11-[4-[2-[2-(triphenylmethoxy)ethoxy]ethyl]-1-piperazinyl]- (CA INDEX NAME)

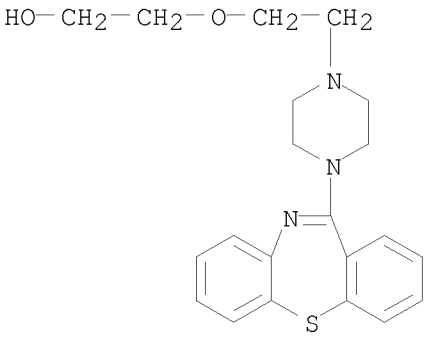


IT 844639-07-2P, 11-[4-[2-(2-Acetoxyethoxy)ethyl]piperazin-1-yl]dibenzo[b,f][a,4]thiazepine
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and basic hydrolysis of; procedure for preparing quetiapine from a
dibenzothiazepine piperazinoethanol derivative)
RN 844639-07-2 CAPLUS
CN Ethanol, 2-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]-, 1-acetate (CA INDEX NAME)



IT 111974-69-7P, Quetiapine
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, with fumaric acid; procedure for preparing quetiapine from a dibenzothiazepine piperazinoethanol derivative)
RN 111974-69-7 CAPLUS
CN Ethanol, 2-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]-

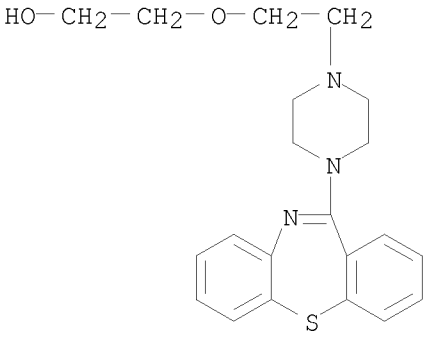
(CA INDEX NAME)



IT 111974-72-2P, Quetiapine hemifumarate
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and reaction of, with fumaric acid; procedure for preparing quetiapine from a dibenzothiazepine piperazinoethanol derivative)
RN 111974-72-2 CAPLUS
CN Ethanol, 2-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]-, (2E)-2-butenedioate (2:1) (CA INDEX NAME)

CM 1

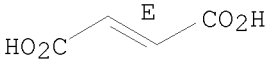
CRN 111974-69-7
CMF C21 H25 N3 O2 S



CM 2

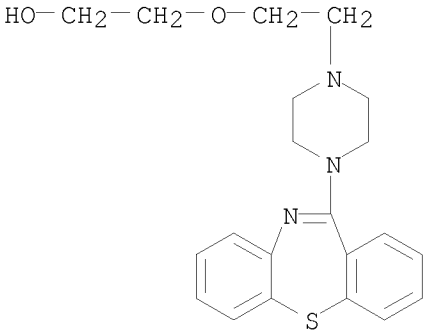
CRN 110-17-8
CMF C4 H4 O4

Double bond geometry as shown.

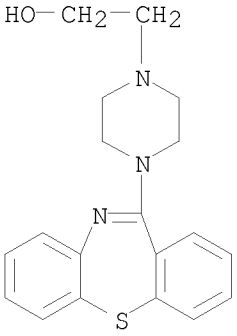


OS.CITING REF COUNT:	1	THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT:	3	THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 16 OF 16 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2001:6274 CAPLUS
DOCUMENT NUMBER: 134:216805
TITLE: Behavioral Approach to Nondyskinetic Dopamine Antagonists: Identification of Seroquel
AUTHOR(S): Warawa, Edward J.; Migler, Bernard M.; Ohnmacht, Cyrus J.; Needles, Ann L.; Gatos, George C.; McLaren, Frances M.; Nelson, Cynthia L.; Kirkland, Karen M.
CORPORATE SOURCE: Departments of Medicinal Chemistry Pharmacology and Drug Disposition and Metabolism, AstraZeneca Pharmaceuticals LP, Wilmington, DE, 19850-5437, USA
SOURCE: Journal of Medicinal Chemistry (2001), 44(3), 372-389
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A great need exists for antipsychotic drugs which will not induce extrapyramidal symptoms (EPS) and tardive dyskinesias (TDs). These side effects are deemed to be a consequence of nonselective blockade of nigrostriatal and mesolimbic dopamine D2 receptors. Nondyskinetic clozapine (1) is a low-potency D2 dopamine receptor antagonist which appears to act selectively in the mesolimbic area. In this work dopamine antagonism was assessed in two mouse behavioral assays: antagonism of apomorphine-induced climbing and antagonism of apomorphine-induced disruption of swimming. The potential for the liability of dyskinesias was determined in haloperidol-sensitized Cebus monkeys. Initial examination of a few close congeners of 1 enhanced confidence in the Cebus model as a predictor of dyskinetic potential. Among dibenzodiazepines, 1 did not induce dyskinesias whereas its N-2-(2-hydroxyethoxy)ethyl analog was dyskinetic. The emergence of such distinctions presented an opportunity. Thus, aromatic and N-substituted analogs of 6-(piperazin-1-yl)-11H-dibenz[b,e]azepines and 11-(piperazin-1-yl)dibenzo[b,f][1,4]thiazepines and -oxazepines were prepared and evaluated. 11-(4-[2-(2-Hydroxyethoxy)ethyl]piperazin-1-yl)dibenzo[b,f][1,4]thiazepine was found to be an apomorphine antagonist comparable to clozapine. It was essentially nondyskinetic in the Cebus model. A number of N-substituted analogs were found to be good apomorphine antagonists but all were dyskinetic.
IT 111974-69-7P 329216-67-3P
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of piperazinyl dibenzazepines as nondyskinetic dopamine antagonists)
RN 111974-69-7 CAPLUS
CN Ethanol, 2-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]- (CA INDEX NAME)



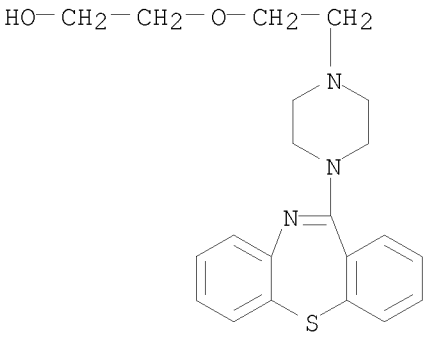
RN 329216-67-3 CAPLUS
CN 1-Piperazineethanol, 4-dibenzo[b,f][1,4]thiazepin-11-yl- (CA INDEX NAME)



IT 111974-72-2P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of piperazinyl dibenzazepines as nondyskinetic dopamine antagonists)
RN 111974-72-2 CAPLUS
CN Ethanol, 2-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]-, (2E)-2-butenedioate (2:1) (CA INDEX NAME)

CM 1

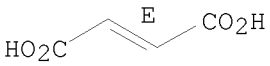
CRN 111974-69-7
CMF C21 H25 N3 O2 S



CM 2

CRN 110-17-8
CMF C4 H4 O4

Double bond geometry as shown.



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REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT